Marlow, R. D., Metz, J., Chesshyre, E., Sarra, A., & Finn, A. (2017). Recent developments in immunisation practice. *Paediatrics and Child Health*, *27*(3), 102-108. https://doi.org/10.1016/j.paed.2016.12.005

Recent developments in immunisation practice

Robin Marlow, Jane Metz, Emily Chesshyre, Katerina Sara, Adam Finn

Bristol Children's Vaccine Centre, University of Bristol and Bristol Royal Hospital for Children, UK

Abstract

Over the last 5 years the UK has led the world in the introduction of new vaccines with substantial changes in the childhood vaccination schedules. These have been both in response and in anticipation of changes in the epidemiology of illness and demonstrate the importance of public health screening and the notification of infectious diseases. This review article briefly outlines the rationale and history behind these most recent developments and highlights potential changes on the horizon.

Keywords: vaccines, rotavirus, influenza, meningococcus, pertussis

ROTAVIRUS

Epidemiology. Rotavirus (RV) is the single most important cause of infectious diarrhoea in young children worldwide and is responsible for almost a half a million deaths each year. Mortality related to RV infections is almost exclusively in resource-poor countries. In wealthier societies without high uptake vaccine programmes the infection remains common and the accompanying morbidity results in much distress and suffering as well as significant healthcare and societal pressures and costs. In temperate regions, RV infection occurs in annual epidemics usually peaking in early spring. Almost all children will have encountered the disease at least once by the age of five and the majority before the age of two. The virus is transmitted via the faeco-oral route and is abundantly excreted in stool during and sometimes for several weeks after the resolution of clinical symptoms. As few as ten viral particles are sufficient to cause clinical disease in susceptible individuals, which makes reliable prevention of spread of the infection by hygiene measures effectively impossible.

Vaccines. The early history of RV vaccines had a profound effect on their subsequent development and uptake. In the 1990s the first licensed oral RV vaccine (RotaShield® Wyeth) completed phase III trials and rapidly went into use in the USA. However after nine months post-marketing surveillance suggested clustering in incidence of intussusception (IS) particularly in the period following the first dose in vaccinated individuals, leading to the voluntary withdrawal of the vaccine from the market. Nearly ten years later in 2006, two new live oral vaccines were licensed in Europe, Rotarix (GlaxoSmithKline Biologicals) and RotaTeq (Merck & Co, Sanofi Pasteur-MSD).

Rotarix is a monovalent attenuated human RV strain given to infants 6 – 24 weeks of age as two oral doses at least four weeks apart. The phase III trial in >63,000 children reported no increase in rates of IS, 85% effectiveness against hospital admissions and 85% against severe disease and up to 100% against very severe disease. An efficacy trial carried out in South Africa and Malawi reported 61.2% efficacy against severe disease and although it was lower in the more resource-poor Malawi (49.4%

vs. South Africa 76.9%), the impact on mortality there was predicted to be higher due to higher burden of disease there.

RotaTeq is a pentavalent vaccine combining human-bovine reassortant strains and is given to infants 6–33 weeks of age as three oral doses at least 4 weeks apart. Pre-licensure studies in >69,000 children also showed no increase in rates of IS, 74% protection against all RV gastroenteritis and 98% protection against severe disease with an almost 95% reduction in emergency room attendance and 86% reduction in missed work days by parents of vaccinated children. Large efficacy trials in Asia and sub-Saharan Africa found 48.3% and 39.3% protection against severe disease. The consistent finding of reduced efficacy in countries with lower socio-economic status is still not clearly understood and is likely to be multi-factorial. Proposed contributing factors are higher rates of breastfeeding (containing higher titres of anti-rotavirus antibodies), oral polio vaccine use, higher prevalence of other viral and bacterial gut infections, malnutrition and other socio-economic factors. Nevertheless because of high RV mortality rates in these countries, it is here that the vaccines have the potential to prevent hundreds of thousands of diarrhoea-related deaths.

Approaches to roll out. In 2009 the World Health Organization (WHO) - Strategic Advisory Group of Experts (SAGE) recommended that RV vaccine be introduced to all countries' immunisation programmes. But the decision to implement this advice is influenced by each country's healthcare system and burden of disease. In regions such as Western Europe that have low rates of mortality, inclusion has been gradual with only 7 countries currently giving RV vaccine routinely, although in most of the others the vaccines are also available privately – usually resulting in limited coverage and so few herd effects. Almost all mortality from RV occurs in the very poorest countries and the Global Alliance on Vaccines and Immunisation (GAVI) was set up with the aim of meeting the Millennium Development Goal 4 – reduction of childhood mortality. They have pledged to give financial support to help introduce childhood vaccines in a sustainable way, pooling demand to shape vaccine markets and helping fund vaccines though a co-payment process. By supporting the upfront cost of vaccine introduction, the hope is that resulting socio-economic and healthcare savings will facilitate ongoing use. GAVI has been able to secure RV vaccines at $5 per course compared to around €45 per dose on the open market. Eligible countries can then obtain them from GAVI from just $0.20 per dose. Of the 81 countries now including rotavirus vaccines in their routine schedule (figure 1), 31 are supported by GAVI.

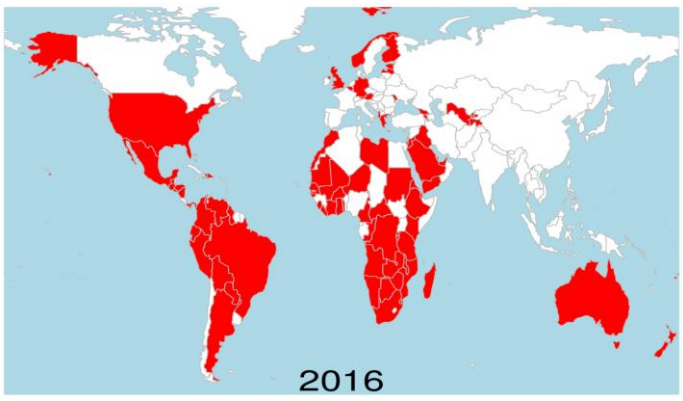


Fig 1: Current Worldwide use of RV vaccine – data source World Health Organization

Intussusception. Although both the large pre-licensure trials did not detect any increase in rates of IS, since the two current vaccines were introduced to widespread clinical use, national surveillance data from Australia, Mexico, Brazil and the USA have shown convincing evidence of an association for both of them at a rate of around 1 in 50-100,000. It remains unclear whether these represent additional cases or precipitation of cases that would otherwise have occurred later. The current position of the WHO Global Advisory Committee on Vaccine Safety (GACVS) is that "based on available evidence, the benefits of RV vaccination to all infants, without age restriction, would greatly exceed the risks, particularly in developing countries with moderate and high mortality from RV disease".

Implementation and impact. The UK introduced Rotarix into the routine childhood schedule in July 2013 and rapidly achieved 98% first dose coverage. The first season after introduction saw estimated reductions of up to 150,000 general practice attendances, 35,700 ED attendances and 8,120 admissions to hospital. A population case control study identified an increased risk of intussusception in the 1-7 days after vaccination with an estimated additional 21 cases following vaccination, all of whom were treated successfully. Experience in similar high income countries such as the USA, Australia, Israel, Belgium, Austria, Luxembourg and Finland which have introduced routine RV vaccination, shows it to be highly effective (90% prevention of hospital admission) and to result in large reductions in healthcare costs. In middle and lower income countries it has been shown to have profound effects on childhood mortality. In Mexico a 46% reduction in under five mortality due to gastroenteritis has been shown. Early post implementation data from the GAVI countries is also positive with reports of reductions in rates of hospitalisation by 50% and vaccine effectiveness estimated at 65%.

There are many low cost high volume alternatives vaccines at varying stages of development. Notably India has developed its own, costing $1 per dose. Injectable inactivated vaccines are also in very early development and with proposed benefits such as increased heat stability, lack of association with IS and less vulnerability to environmental interference, they may ultimately prove to be an effective alternative approach.

With the current vaccines now having been in use for ten years and with many millions of doses given, no new problems with serious side-effects or strain switching have materialised to date. In high income settings significant economic savings have been seen consistently while in low resource settings there have been significant reductions in mortality. With so many countries of the world now sparing their children from this disease, it will be of interest to observe how long it takes the rest to follow suit and introduce universal infant vaccination against RV.

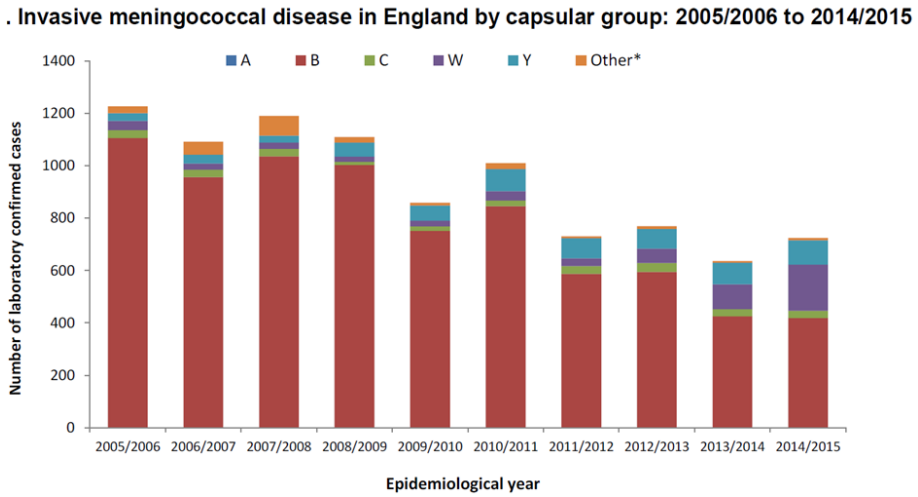
MENINGOCOCCUS

Despite a substantial reduction of annual laboratory-confirmed cases of invasive meningococcal disease (IMD) in the UK over the past 15 years (2448 in 2000-2001 to 724 of 2014-2015, epidemiological year, July-June), IMD remains the leading infectious cause of death in early childhood and causes significant morbidity and mortality, especially in young infants where 5-10% of victims do not survive and up to 20% suffer from serious sequelae including limb loss and seizures while up to 57% suffer from cognitive impairments

The burden of meningococcal disease is greatest in young children, with half of cases currently diagnosed in those less than 5 years of age. This is therefore the population in greatest need of direct protection. Incidence rates are also somewhat higher in late adolescence and among the elderly than during the rest of adult life. The nasopharynx provides a stable ecological niche for meningococci and humans are the only known animal hosts. Eliminating carriage would therefore eliminate disease. Vaccination with conjugate vaccines against meningococcal disease has been shown to impact on carriage. However meningococcal carriage is rare in early childhood and commoner in adolescents and young adults; rates as high 55% have been reported in university students.

Meningococcus can be divided into strains based on the characterisation of its polysaccharide capsule. The relative rates of each group have risen and fallen over time with the emergence of strains with varying invasive potential (see below).

Figure 2. Taken from PHE Health Protection Report Oct 2015



Some of these declines can be partially explained through changing behaviours such as reduced smoking rates but fundamentally they remain driven by a poorly understood complex interaction between population immunity and meningococcal bacteria, which lead to the arrival and eventual disappearance of various clones with differing predisposition to cause disease.

In 2015, the UK became the first country in the world to have a comprehensive routine meningococcal vaccine programme targeting all of the main disease-causing capsular groups of *N. meningitidis* (A, B, C, W and Y). The meningococcal immunisation schedule against the different capsular groups targets both age groups and populations at highest risk of disease to provide direct protection and those with highest carriage rates to reduce transmission and confer indirect protection (herd immunity), approaches which are under continuous review by the UK Joint Committee on Vaccination and Immunisation (JCVI).

Men C

The glycoconjugate **Men C** was the first universal meningococcal vaccine to be introduced by the UK National Health Service (NHS) in 1999. The programme in infants, alongside a large catch up programme for all children and adolescents, was in response to a rapid rise in IMD cases caused by a

single Men C clone (part of the ST-11 complex) which was associated with a high case fatality rate. This successfully controlled the outbreak and resulted in sustained population protection against Men C over the past 15 years with clear evidence of reduced rates of asymptomatic colonisation with this serogroup. The current Men C immunisation schedule not longer includes infants with doses only at 12 months and 13-14 years. The adolescent booster was added to secure enduring herd protection as the year 2000 catch up cohort aged and was supported by evidence that vaccination at this age was very immunogenic with good antibody persistence. In 2015 this adolescent booster was changed from monovalent Men C to quadrivalent Men ACWY conjugate vaccine as discussed below.

Men B

In England, Men B is the main cause of IMD although prior to Men B vaccine introduction, there was a significant reduction in the absolute number of IMD caused by Men B, from 1614 cases in 2000/2001 (epidemiological year, July to June) to 418 cases in 2014/2015(see figure 2). After more than two decades of clinical development, a multi-component Men B (4CMenB) vaccine was licensed by the European Medicines Agency in early 2013, and in September 2015 a long awaited national infant vaccine programme against Men B was launched in the UK. The vaccine is included in the primary immunisation schedule at 2, 4 and 12 months of age. At present, there is no adolescent booster or catch-up programme.

The Men B vaccine was difficult to develop; Men B capsular polysaccharide, unlike the other meningococcal groups is poorly immunogenic and identical saccharides are found on human foetal neural cell adhesion molecules (and are thus self antigens). Significant antigenic diversity among endemic Men B strains has complicated selection of subcapsular Men B antigens for vaccine development. The 4CMenB vaccine comprises four components; three are recombinant meningococcal surface antigens, the fourth an outer membrane vesicle (OMV) made by detergent extraction from a strain which caused an extended outbreak in New Zealand where this latter component was used as a stand-alone vaccine. The new Men B vaccine is predicted to cover 73–88% of Men B strains causing invasive disease in the UK with at least one antigen and due to its OMV component may also theoretically have some effect against other groups.

The infant programme is expected to provide direct protection for vaccinated children but little or no indirect (herd) protection. Further work is being undertaken to assess the potential for an adolescent Men B programme that, like the Men C, (and hopefully Men W) immunisation programme, might induce direct and indirect protection. However improved methodology for carriage detection in large-scale vaccine trials will be needed to gather the information required.

Men W

Historically, Men W has been a rare cause of IMD in England and Wales, accounting for <5% of all laboratory-confirmed cases but more recently, this has changed (Figure 3).

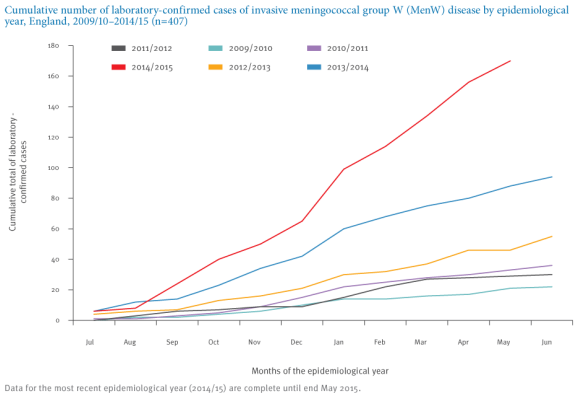
In 2000-2001 there was a Men W outbreak among people returning from the Hajj pilgrimage accounting for 127 of 2448 cases (5.2%) during this period. This outbreak was controlled by mandatory Men ACWY vaccination of all pilgrims entering Saudi Arabia; by 2008-2009, the percentage of IMD caused by Men W had returned to baseline (21 of 1164 cases, 1.8%). Since 2009–

2010, cases are again increasing, nearly doubling annually to 2015 (Figure 4) and associated with a case fatality rate (12%) which is significantly higher than that reported for Men B. This increase has extended across all age groups, including adolescents (15–19 year-olds) and infants and none have been epidemiologically linked to Hajj travel since mandatory vaccination of pilgrims. Genome testing of Men W IMD cases has shown they belong to cc11 strain; this strain is very similar to the one responsible for recent South American outbreaks, associated with a very high case fatality rate (31% in Chile). Worryingly in both countries, this strain has been associated with atypical presentations: a retrospective study of confirmed Men W cases in 2012, found a low frequency of meningeal signs but nearly 50% of patients presenting with gastroenterological symptoms. After fever, diarrhoea was the second most frequent symptom among deceased patients (55.6%) and statistically higher than survivors (26.8%).

Following JCVI recommendations, the UK national outbreak response has been rapid introduction of an adolescent Men ACWY conjugate vaccine programme from August 2015 replacing the Men C only booster. In addition to providing direct protection against these capsular groups, it is expected that, by reducing carriage rates, other age groups may be protected indirectly over the coming years provided sufficiently high uptake rates can be reached.

There are early reports of increasing Men W IMD rates in other European countries alongside novel genetic changes in the circulating invasive strain. Accordingly steps may soon be needed to control the spread of this problem elsewhere.

Figure 3. Taken from Eurosurveillance Campbell et al 2015



The Future

Where meningococcal vaccines induce immune responses which reduce colonisation and transmission, adolescent immunisation may ultimately prove to be the most efficient and cost effective approach to controlling IMD, provided high coverage can be reliably achieved. While there is evidence in support of this approach with conjugate vaccines, more research is needed before it can be used for the newer protein antigen “Men B” vaccines. Careful epidemiological surveillance remains essential as meningococcal disease constantly changes.

Influenza - the introduction of live attenuated influenza vaccine (LAIV) for healthy children

Influenza is one of the main causes of hospital admissions and death due to respiratory illness. It occurs in annual epidemics with different strains, often having undergone genetic drift,

predominating each year in an un-predictable manner, meaning vaccines have to be reformulated for each new season. Children aged under 5 years (especially those aged under 2 years), pregnant women, people aged over 65 years and those with underlying medical conditions are especially prone to complications caused by influenza. The UK has recommended vaccination of at risk populations since the 1960s but has recently extended the indications to include otherwise healthy young children.

Children spread influenza to healthy individuals more easily than adults, as the viral load in their secretions is both higher and excreted for longer periods of time. Thus, it is thought that seasonal influenza epidemics are driven in the community by infection of and among children. Preventing the disease in this age group with an effective immunization programme could have an enhanced public health impact by also reducing rates of infection in other age and risk groups.

In 2012, after reviewing from a dynamic transmission model, the UK JCVI, recommended annual vaccination of healthy children from the age of two years with live attenuated influenza vaccine (LAIV). Live cold adapted strains of influenza virus given by intranasal spray stimulate an immune response in the upper airways but are unable to replicate in the warmer lower respiratory tract. The efficacy this vaccine in children is well documented in a series of randomized controlled trials versus placebo and inactivated injected flu vaccine (IIV). The vaccine is safe with the most common adverse reactions being mild transient nasal congestion or low grade temperature. However studies have found a higher rate of wheezing in very young children so in both Europe and the USA it is not recommended for children under 2 years old or for children and adolescents with severe asthma or active wheezing. Children at high risk with contraindications to LAIV or under the age of 2 years are still recommended to receive IIV.

Introduction was planned as a staged rollout. During the first (2013/14) influenza season a single dose of LAIV was offered to all children aged two and three years and in seven pilot areas to primary school aged children of four to eleven years. Vaccine uptake in the pre-school age children was 41.1% and in pilot areas 52.5%. Influenza activity was unusually low during this season and it was difficult to evaluate vaccine effectiveness (VE) fully. However although not statistically significant, there was a consistent decrease in measures of disease between pilot and non-pilot regions supporting of the continuation of the programme.

During the second season of rollout (2014/15) all healthy two to four year old children were offered LAIV vaccination. The 2013/14 primary school pilot areas continued vaccination with new pilot areas now also offering the vaccine to secondary school age children. In the preschool cohort uptake levels were 37.6%. Rates were higher in the school based pilot areas, 56.8% and 49.8% in primary and secondary schools respectively than in areas using primary care or pharmacy-based delivery. During this season the flu activity was moderate. Although the dominant strain subtype (H3N2) was contained in the vaccine, it had undergone antigenic drift from the predicted strain, reducing VE. According to the end of season studies the overall adjusted VE in children was 17.5 % (95 % CI: -41.1 - 51.7) for influenza A and 19.1 % (95 % CI: -44.1 - 54.6) for influenza A (H3N2).

During the third season (2015/16) LAIV roll out was extended from all children two to four years old to school years 1 and 2 (5-7 years). In Northern Ireland and Scotland all primary school age children were offered vaccination. Coverage again was again low in preschool children (34.3%) and higher in schools (53.7%). The main circulating strain was A (HINI)pdmo9. In children, overall VE

against laboratory-confirmed influenza was 57.6% (95% CI: 25.1–76) and 41.5% (95% CI: −8.5 to 68.5) for the dominant influenza A(H1N1)pdm09. Interestingly these findings are in contrast with the 2015/16 VE reports from the CDC in the USA where VE of only 3% (-49% – 37%) for LAIV was reported compared to 63% (52%-72%) for IIV. Recommendations to use LAIV there have been withdrawn in the 2016/17 season. The reasons for this disparity are as yet unknown but results from other countries using LAIV such as Finland and Canada have been concordant with UK experience.

Over the first three seasons of use in the UK, LAIV has shown superior VE to IIV in children 53.1% (95% CI: 31.4–67.9) vs 31.5% (95%CI: −50.4–68.8). But despite mismatched years, limited roll out and coverage issues, there has been some evidence of the anticipated herd effects in other age groups, particularly in areas of high coverage such as Scotland and Northern Ireland. In 2016/17 the programme will continue to extend, vaccinating those from 2 years old to school year 3 (7-8yrs) with a target of 40-65% coverage. The models suggest that this public health strategy has the potential for drastic reductions in influenza transmission in the UK, not only protecting those vulnerable to severe complications of influenza but improving the health of the entire community.

Pertussis

Bordetella pertussis is the most common vaccine preventable disease, despite generally high vaccine uptake, with recent epidemics, for example, in USA in 2012, UK in 2012 and Argentina in 2011. Incidence of pertussis have been increasing in many countries over the past 30 years, trends that started prior to, and accelerated following, the switch from whole cell pertussis (wP) vaccine to acellular pertussis (aP) vaccine in many primary immunisation schedules. This was done in many countries in the 1990s-2000s due to significant local and systemic side effects rates of wP vaccine; continued use of which could have threatened public confidence in immunisation programmes in general and latterly to the unavailability of wP-containing combination vaccines. Reasons for this resurgence are thought to be a combination of better clinical case recognition especially in older age groups, better diagnosis especially with increased availability of reliable detection using PCR, patchy vaccine coverage in some areas and principally reduced duration of protection following aP vaccination compared to wP and both vaccine types compared to immunity following infection, leading to infection and transmission among previously vaccinated people. There is also evidence from research in non-human primates that wP vaccines may have a greater impact upon transmission of the infection than aP vaccines. Finally there is some evidence of emergence of vaccine escape mutants. A major effort is now needed to improve pertussis control tools. Possible strategies include adjuvanted vaccines, development of novel vaccine antigens including live attenuated vaccines and, in the meantime, improved strategies for deployment of existing vaccines.

Aspects acellular pertussis (aP) vaccine- induced immunity

aP vaccines contain only 1-5 pertussis antigens whereas wP vaccines contain the whole organism and so thousands of antigens which may broaden protection and also have adjuvant effects. *Bordetella pertussis* strains lacking pertactin, an antigen included in most aP vaccines, have been reported circulating in Europe, Australia, Japan and the USA. These strains may have a selective advantage in highly immunised populations.

Observational studies suggest waning immunity following aP vaccination, with children up to 15 times more likely to acquire pertussis 5 years, as compared to 1 year, following the 5th aP dose.

Animal studies suggest that the reason for this is that aP induces a CD4+ T helper (Th) 2 dominated immune response, whereas wP vaccines and natural infection induce a mixed CD4+ Th1/ Th17 response. These distinct types of immune response have been shown following aP and wP vaccination in mice, baboons and children. Observational studies also suggest that individuals primed with aP were 2 to 5 times more likely to develop pertussis subsequently compared to those primed with wP suggesting that the immunological character of the initial response may endure to an extent regardless of subsequent exposure to vaccine boosters or infection.

Large clinical trials prior to the implementation of aP vaccine and a recent Cochrane review have shown that aP vaccination is up to 85% effective in preventing pertussis disease; however it may not prevent asymptomatic, or mildly symptomatic infection. This has been shown in the baboon model of pertussis where those vaccinated with aP vaccine, although protected from severe disease, were not protected from infection and were able to transmit infection to others; whereas wP vaccinated baboons cleared infection twice as fast. This hypothesis is supported by observational data in humans showing that infection continues to circulate especially in some aP-vaccinated populations; and that epidemiological peaks following periods of low vaccination suggest that aP vaccination can effectively control numbers of severe cases of disease but total numbers of cases to a much lesser extent.

Strategies to improve the effectiveness of *B. pertussis* vaccination

A short term option is to give additional boosters with the current combined aP vaccines (DTaP/IPV: Diphtheria, Tetanus, acellular Pertussis, inactivated polio vaccine) to targeted populations such as pregnant women from 20 weeks gestation. The aim of vaccinating pregnant women is to reduce disease in infants who have the highest mortality from pertussis, by reducing disease in mothers thereby interrupting transmission to their infants and by protecting the infant with passive antibody transfer from the mother via the placenta and breast milk. This strategy has been shown to be highly effective at reducing infant deaths in the UK in case control studies. Mothers are recommended to have further doses in subsequent pregnancies and although problems with adverse reactions to repeated doses have not been reported this remains a theoretical concern. Other strategies that have been proposed and, in some cases, implemented but only with limited success include: single adolescent or single or regular adult booster doses of DTaP, vaccination campaigns in response to outbreaks, immunisation of family contacts around newborns (the so-called cocooning strategy) and the production of aP only pertussis vaccines for use where boosters of other antigens are not necessary.

A longer term solution is the development of a 3rd generation of more effective vaccines to protect against disease and carriage and give longer lasting immunity to pertussis, without the side effects of wP vaccine. A less complex option might be to modify existing vaccines. Reducing the content of endotoxin in the wP vaccine to make it less reactogenic has been proposed. Adapting aP vaccines by adding new antigens such as adenylate cyclase toxin, iron regulated proteins or the autotransporter BrKA are options as is adding to or replacing the aluminium adjuvant of existing aP vaccines with biological agents such as Toll- like receptor (TLR) agonists which can induce Th1 responses in mice. Following pre-clinical studies in mice showing Th1 responses, a live attenuated vaccine BPZE1 is in early phase clinical trials, being given intranasally (to target respiratory mucosal immunity) in adult volunteers. Both safety and efficacy would need to be shown in follow up studies. Vaccination with

an aP nanoparticle vaccine composed of outer membrane vesicles given intranasally to mice produced a mixed Th1/Th2 response and good antibody response and has the potential to protect against both *B. pertussis* and *parapertussis*.

Conclusions

Widespread resurgences of pertussis despite high vaccination coverage are a serious problem. Current vaccination schedules, particularly those using aP vaccines, can result in ongoing circulation of pertussis despite high uptake and coverage. Development of new vaccines is challenging and will take time and demonstration of efficacy will be challenging in the absence of large unvaccinated populations. The WHO has recommended that countries using wP schedule should not switch to aP schedules for the time being while more research is done. These challenges are occurring on the background of severe supply shortages of pertussis containing vaccines in many areas. The one notable recent success has been the demonstration that fatal pertussis in early infancy can be reliably be prevented by immunisation of pregnant mothers with aP containing vaccines. This strategy is being adopted in many areas where significant numbers of infant cases are occurring. However, while it can prevent the worst cases and deaths, it will do little or nothing to reduce the broader circulation of pertussis in the community and so the risks remain.

Final conclusions

Over the last 5 years the UK has led the world with several introductions and effective implementations of childhood (and maternal vaccinations) as both reactive and pre-emptive modification of the vaccine schedule to optimise protection. With the clear successes of rotavirus and maternal pertussis vaccination programmes and early evidence of the impact of influenza and MenB programmes, the question becomes what next? Both universal hepatitis B and varicella vaccines have been shown to be very effective when used in other countries and the UK will introduce the former into the primary schedule in 2017 and is re-evaluating the latter. The importance of retaining high vaccination coverage can be seen with large UK measles outbreaks in 2013 as a result of the MMR vaccine scare of the 1990s and early 2000s and recent similar and equally unfounded collapses in public confidence in the HPV vaccine programmes in Denmark and Ireland which will doubtless result in many unprevented cases of malignancy and genital warts in those countries in the future. As public perception of the risks of infectious diseases fall, the paediatrican's role as childrens' vaccine advocates becomes ever more vital.

Further reading – probably allowed max of 6-8.

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